REMARKS

Claims 1-25 and 27-47 are pending. Claims 48-61 have been added and claims 19-21, 31, and 45 have been cancelled. Claims 1-3, 12-18, 28, 30, 36-43, and 47 have been amended. Therefore claims 1-18, 22-25, and 27-30, 32-44, and 46-61 are pending in the Application.

Support for these amendments can be found throughout the specification, e.g., at page 2, lines 20-22, and pages 14-15, examples 33, 39, 42, 44, and 46 and in claims 1-27 as originally filed. Support for new claims 48-61 can be found throughout the specification and claims 1-18 as originally filed of the following Applications from which priority has been claimed and acknowledged: Swedish Patent Application No. 0003810-9 and United States Provisional Application No. 60/243,115, both of which are incorporated by reference in their entirety in the instant Application. No new matter is introduced by these amendments.

Applicants acknowledge that the Examiner has allowed claim 32 in the Office Action dated April 28, 2003 (the "Action).

Priority Claim

According to the Action, Applicants' claim for priority under 35 U.S.C. 119(a)-(d) based on Swedish Patent Application No. 0003810-9 is acknowledged, however, the 003810-9 Application fails to provide adequate support under 35 U.S.C. 112 for claims 1-18 and 20-47 of the instant Application (Action, part 3). Specifically:

> The present claims are to molecules with 12 different heterocyclic radicals attached either to position 4, position 5, or both positions of an indole core. Swedish Application 0003810-9 discloses indole compounds with only nine different heterocyclic radicals attached only to position 4 of an indole core. A benzyl group is a presently claimed substituent on these heterocyclic radicals. In the Swedish Application it is not (Action, page 3, lines 10-14).

Applicants first point out that the '115 Specification teaches that "R^4 = H, or the following amine groups" ('115 at page 3, line 9). Second, the amine groups recited as possible R^4 substituents are all nitrogenous heterocycles that fall within Applicants' definition of

"heterocyclyl" ('115 Application at page 3, line 10 and the instant Application at page 4, lines 15-22). Finally, the '115 specification also teaches that "$R^5 = R^4$ or H, hydroxy, C_{1-3} alkoxy, F, NO_2, CF_3, OCF_3" (emphasis added, '115 Application, page 3, line 9). Therefore, because R^5 can be any substituent defined in R^4, and R^4 can be heterocyclyl, then the priority documents do, in fact, teach attachment to both position 5 and position 4 of the indole core. Applicants also point out that the '115 Application discloses 1-(phenylsulfonyl)-5-(1-piperazinyl)-1H-indole as a particularly preferred embodiment ('115 Application at page 3, line 9). The teachings of the Swedish priority document embrace indoles having heterocyclyl radicals attached to positions 4 and/or 5 of the indole core and are therefore not limited to indole compounds with heterocyclic radicals attached only to position 4 of the indole core as stated in the Action. Thus, Applicants respectfully submit that compounds having heterocyclyl radicals at R^4 and/or R^5 be accorded the earliest effective filing date of October 20, 2000.

According to the Action, Applicants' claim for priority under 35 U.S.C. 119(e) based on United States Provision Application No. 60/243,115 (the '115 Application) is acknowledged, however, it is alleged that the '115 Application fails to provide adequate support under 35 U.S.C. 112 for claims 1-18 and 20-47 of the instant Application (Action, part 3). As the disclosure of the '115 Application is the same as that of the Swedish Application, Applicants again respectfully submit that compounds having heterocyclyl radicals at R^4 and/or R^5 be accorded the earliest effective filing date of October 20, 2000 for the reasons set forth above.

Rejections under 35 U.S.C. 112, Second Paragraph

Claims 24 and 25 remain rejected because the phrases "a disease mediated by the serotonin-related 5-HT6 receptor" and "a CNS disorder" are indefinite (Action, part 7). New claims 34, 35, 44, and 45 are also rejected on the same grounds. According to the Action, the references provided by Applicants in the response filed on February 5, 2003 (along with a reference cited by the Examiner) do not provide an adequate consensus of what particular diseases are covered by the above phrases, the rejection concluding with the statement "With such contradictions it is clear there is no art recognized list of such diseases" (Action, page 6, lines 2-3).

Applicants respectfully traverse. A definite claim is a claim that apprises one of ordinary skill in the art of its scope and serves notice to others as to what constitutes infringement of the patent (MPEP 2173.02). Applicants have provided evidence in both the instant specification and in the previous response that one of ordinary skill in the art would fully appreciate and understand the meaning of "a disease mediated by the serotonin-related 5-HT6 receptor" and "a CNS disorder." Applicants thus submit that the claims are definite and meet the statutory requirements of 35 U.S.C. 112, second paragraph. With regard to theconclusory assertion which quote that "there is no art recognized list of such diseases, Applicants submit that the fact that a collection of skilled artisans does not each produce fully overlapping lists of medical indications that pertain to "a disease mediated by the serotonin-related 5-HT6 receptor" or "a CNS disorder does not support a finding that the art does not recognize such diseases. Just the fact that a disease is mentioned once by someone in a peer-reviewed journal article (including those cited in the Action and in the aforementioned response) as being associated with a 5-HT6 receptor or a CNS disorder indicates that it would be recognized by one of ordinary skill as being a 5-HT6 receptor or CNS disorder.

Rejections under 35 U.S.C. 112, First Paragraph

Claims 24, 25, 27, 44, and 45 are rejected for not reasonably providing enablement for treating "every CNS disorder" or "every disease mediated by the serotonin-related 5-HT6 receptor." According to the Action:

> Determining if any particular claimed compound would treat every CNS disease or 'disease mediated by the serotonin-related 5-HT6 receptor' would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it [to, *sic*] clinical trials with a number of fundamentally different diseases which occur in the brain and spinal column, a large degree of experimentation (emphasis added, Action, page 7, lines 8-11)...The scope of the claims involves all of the hundreds of thousands of compounds of claim 1 as well as the hundred of thousands of diseases embraced by the term CNS diseases. Thus undue experimentation will be required...(emphasis added, Action, page 9, lines 1-3).

Applicants submit that the experimentation that may be required to embrace the scope of the invention may rise to the level of extended experimentation, but not to the level of undue experimentation. It is held in *In re Colianni* and *In Re Wands*:

> [A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance (In *In re Colianni*, 195 USPQ, 150, 153, (CCPA, 1977)).
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine (*In Re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988))

With regard to points (a), (b), and (h) in part 8 of the Action, Applicants submit that the steps delineated in the first passage from the Action are certainly routine steps practiced in the process of drug discovery and development by one of skill in the art. Further, ample guidance and direction is provided in the instant specification in the form of a roadmap of preferred compound attributes, exemplary compounds, and synthesis and test methods so that a skilled artisan could make and use the claimed invention without undue experimentation.

Applicants also disagree with the assertion in the Action that "clinical trials with a number of fundamentally different diseases" are a necessary requirement for determination of enablement. It is well established that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlative to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing PTO decision based on finding that *in vitro* data did not support *in vivo* applications)." See MPEP 2164.02. Moreover, "[o]ffice personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." MPEP 2107.03(IV). Applicants further point out that the assertion in the Action that the term "CNS diseases" embraces "hundred[sic] of thousands of diseases" is not supported by any

stated evidence, and absent such support, perhaps overstates the breadth asserted. With regard to part (b), Applicants point out that the selection of dosages is within skill of the art and may be determined by a physician based on the physical profile of the subject and guided by clinical results conducted under the auspices of Food and Drug Administration review. In point (c), the absence of a working example involving man or animals is noted. Applicants point out that while such a showing is not required and does not automatically lead to a finding of lack of enablement, the presentation of an *in vivo* or *in vitro* animal model that "correlates" with a disclosed or claimed method can constitute a working example (see MPEP § 2164.02). As indicated in the Action, Applicants present an obesity related disease model (ob/ob mouse) at page 61, line 21 through page 63, line 10 of the Specification as a model to correlate with reduction of food intake. Thus, Applicants have presented a working example in the context of MPEP § 2164.02.

With regard to point (e), Applicants disagree that the Robichaud passage referred to in the action establishes that the claimed methods fall within the practice of an unpredictable art. Applicants also disagree with the statement in the Action that "[t]he final part of the preceeding sentence makes clear that in 2000, experimental work was under way to determine if selective binding agents were useful therapeutically but as of that date none were understood to be so." (Action, at page 8) Applicants submit that this statement is a misinterpretation of Robichaud and an unsupported extrapolation of the state of the art. The statement in Robichaud that "[t]here exists an array of nonselective agents such as antidepressants, antipsychotics and ergolines that bind to the 5-HT6 receptor with excellent affinity" (including the marketed drug clozapine) provides no indication one way or the other whether selective binding agents were known to be useful. Moreover, whether any agent is either selective or nonselective is not necessarily indicative of its usefulness as a therapeutic. In fact, either may be useful. Further, continued reading of Robichaud after the cited sentence indicates that selective inhibitors were, in fact, known to exist as potential therapeutic agents. Based on the foregoing, Applicants submit that taken together, the state of the art as indicated by Robichaud points to an understanding of 5-HT6 binding compounds (whether selective or nonselective) as being useful as therapeutics.

Finally, there is no evidence within the body of the Action to support the conclusion that the artisan using Applicants invention would be a "physician with a MD degree, board certified in psychiatry and several years of experience" (Action, part 8, section f).

A conclusion of lack of enablement means that based on the whole of the evidence regarding each of the undue experimentation factors, the Specification as the time the application was filed would not have taught one of skill in the art how to make/use the invention without undue experimentation. As discussed above, Applicants' Specification provides ample guidance and direction as to how to make and use the claimed invention including, for example assays based on an art recognized animal model. There is no evidence that the amount of experimentation needed rises above the level of that routinely practiced in the art of drug discovery and development. Finally, the art is both established and progressing, based on references made of record in this Action and in Applicants' responses. Applicants submit that the analysis of the factors weighs on the side of an enabling disclosure and repsectfully requests that the rejection be withdrawn for the aforementioned reasons.

Rejections under 35 U.S.C. 102(e)

Claims 1-4, 6, 7, 9, 11-13, 15, 18, 22-25, 27-31, 33-41, and 44-47 are rejected as being anticipated by Kelly et al., US 2002/0115670 A1 (Kelly). Kelly discloses 1-arylsulfonylindole compounds having piperazinyl, 4-methylpiperazinyl, and 4-benzylpiperazinyl substituents at the 4- or 5-position of the indole ring. Claims 31 and 45 have been cancelled thus rendering the rejection moot with respect to them. Applicants have amended claims 1-3, 12, 13, 15, 18, 28, 38-41, and 47 so as to remove ring-carbon unsubstituted piperazinyl and ring-carbon homopiperazinyl as possible selections for R^4 and ring-carbon unsubstituted piperazinyl as a possible substituent for R^5. Claims 1-3, 12, 13, 15, 18, 28, 38-41, and 47 are therefore not anticipated by Kelly. Since claims 4, 6, 7, 9, 11, and 29 depend from claim 1 and claim 30 depends from claim 28, these claims are also not anticipated by Kelly. Claims 22-25, 27, 33-37, and 44-46 are directed to pharmaceutical compositions and methods of treatment related to compounds of claims 1, 18, 28, 29, and 30 as amended and also are not anticipated by Kelly.

Claims 1-5, 11-14, 18, 22-25, 27, 29, 27, 44, and 46 are rejected as being anticipated by Briggs et al, US 2003/0045527 A1 (Briggs). Briggs discloses 1-arylsulfonylindole compounds having a piperazinyl group at the 4-position of the indole ring. Applicants have amended claims 1-3, 12, 13, and 18 so as to remove ring-carbon unsubstituted piperazinyl as a possible selection for R^4. Claims 1-3, 12, 13, and 18 are therefore not anticipated by Briggs. Since claims 4, 5, 11, and 29 depend from claim 1, these claims are also not anticipated by Briggs. Claims 22-25, 27, 37, and 44-46 are directed to pharmaceutical compositions and methods of treatment related to compounds of claims 1, 18, 28, 29, and 30 as amended and also are not anticipated by Briggs.

Rejections under 35 U.S.C. 103(a)

Claims 1-5, 11, 13, 14, 22, 24, 27, 29, 36, 44 and 46 are rejected as being unpatentable over Isaac et al., *Bioorganic and Medicinal Chemistry Letters*, **2000**, *10*, 1719 (Isaac).

Isaac discloses a hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical (a heterocyclyl radical) attached to an indole, specifically identifying 2-[1-(Naphthalene-1-sulfonyl)-1H-indol-6-yl]-octahydro-pyrrolo[1,2-a]pyrazine as an exemplary species. The heterocyclyl radical is attached to the 6-position of the indole *via* the non-bridgehead nitrogen atom. According to the Action, "The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at position 4 and the reference teaches attachment at position 6. These are *per se* obvious ring position isomers and require no specific teaching" (Action, page 12, part 11).

Applicants respectfully traverse. First, there is no teaching or suggestion in Isaac that would motivate one of skill in the art to synthesize and investigate compounds having the hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical or any heterocyclyl radical at C-4 or C-5 of the indole ring. Isaac clearly focused on other aspects of the molecule, e.g., the nature of the aryl sulfonyl moiety and heterocyclyl ring size and nitrogen content. In fact, the second and third most potent compounds in the study were compounds in which the non-bridgehead nitrogen of the heterocyclyl radical, i.e., the point of attachment of the radical, was replaced by a carbon atom. This data actually teaches away from a basic and essential feature of the instant

compounds, namely attachment of a nitrogenous heterocyclyl to the indole *via* one of the nitrogen atoms.

Second, Applicants further point out that that drug-receptor binding is highly sensitive to substrate molecular geometry. One of skill in the art would recognize that moving the heterocyclyl radical from C-6 to C-4 or C-5 would result in compounds having significantly different shapes, dipole moments, etc. These structural differences can in turn manifest themselves in terms of differences in macroscopic physical properties, e.g., solubilities. No evidence is provided in the Action to establish why a C-6 substituted indole compound would necessarily be expected to function similarly to a C-4 or C-5 substituted indolyl compound.

To further demonstrate their structural/functional differences, Applicants attach as Exhibit A the result of comparative solubility tests carried out with the Issac compound and two of Applicants' claimed 4-substituted indoles, 1-phenylsulfonyl-4-piperazinylindole dihydrochloride (Example 7 in Exhibit A) and 1-[(2,5-dimethoxyphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride (Example 8 in Exhibit A). The results clearly show that an order of magnitude difference in solubility exists between the Issac compound (a 6-substituted indolyl compound) and each of the claimed 4-substituted indoles. Thus, this data provides unequivocal evidence that the C-6 and C-4 indoles exhibit different properties and that the physical properties of a C-4 substituted indole are not predictive of a C-6 substituted indole via simple extrapolation of one set of physical properties to the other.

It is stated in the Action that Isaac "teaches that 'specific concentrations of test compounds' were prepared. These presumably were in water, saline, or buffer and are compositions. Thus, Applicants claims 22 and 46 are made obvious" (emphasis added, Action, page 13, lines 2-5). It is further stated in the Action that "The expectation that compound 4a is useful for treating schizophrenia, depression, and memory dysfunction is taught in the final paragraph on page 1721. Thus Applicants' claims 24, 27, 44, and 46 are made obvious" (Action, page 13, lines 7-9). Applicants have established above that the instant compounds are not obvious over Isaac. The instant compounds are structurally and functionally distinguishable.

Therefore, the methods of treatment and pharmaceutical compositions employing the instant compounds are also not rendered obvious by Isaac.

Finally, the Action states that Isaac is an "enabling disclosure" (Action, page 13, lines 17-18). Applicants note that the synthesis methods disclosed in Isaac describe 6-substituted indoles only. There is no teaching or suggestion in Isaac regarding synthesis of 4- or 5-substituted indoles. Furthermore, Applicants submit that halogen atoms that are *meta* with respect to the indole nitrogen, i.e. C-6, would not necessarily be expected to behave similarly in transition metal mediated aminations, e.g., in the oxidative addition step, than halogen atoms that are *para* with respect to the indole nitrogen, i.e., C-5. There is no evidence or data within the body of the Action to support the conclusion that amination of the Isaac substrates would necessarily suggest the compounds of the instant Application.

Applicants submit for the foregoing reasons, that the assertion of obviousness based on a presumed expectation that structurally similar compounds possess similar properties is incorrect, and particularly here, unsupported. The Office has therefore not established a *prima facie* case of obviousness. Applicants respectfully request that the rejection of claims 1-5, 11, 13, 14, 22, 24, 27, 29, 36, 44 and 46 be withdrawn.

Claims 28, 30, 33-40, and 47 are rejected as being unpatentable over Isaac. According to the Action, "The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at position 5 and the reference teaches attachment at position 6. These are *per se* obvious ring position isomers and require no specific teaching" (Action, page 12, part 11). Applicants submit that the arguments set forth above in response to the rejection of the claims related to the 4-substituted compounds apply similarly here. Applicants respectfully request that the rejection of claims 28, 30, 33-40, and 47 be withdrawn on the same grounds.

Claims 5, 14, and 18 are rejected as being unpatentable over Kelly. According to the Action, Applicants' claimed compound having Ar = naphthyl and R^4 =piperazinyl is a per se obvious ring position isomer of the disclosed Kelly species having Ar = naphthyl and R^5 = piperazinyl (Action, page 15, part 13). Applicants have amended independent claim 1, from

which claims 5 and 14 depend, and independent claim 18 so as to remove unsubstituted piperazinyl as a possible selection for R^4. Kelly does not teach or suggest any of the remaining heterocyclic selections for R^4 or R^5 in the genus delineated in claim 1. Therefore, Applicants submit that Kelly does not render obvious claims 5, 14, and 18.

Claims 18 and 20 are rejected as being unpatentable over Kelly. According to the Action, Applicants' claimed compound having Ar = 2,5-dimethoxyphenyl and R^4 =piperazinyl is a per se obvious ring position isomer of the disclosed Kelly species having Ar = 2,5-dimethoxyphenyl and R^5 = piperazinyl. Applicants have cancelled claim 20 thus rendering the rejection of it moot. Applicants have amended claim 18 so as to remove species having piperazinyl at R^4 or R^5. Kelly does not teach or suggest any of the remaining R^4 heterocyclic groups delineated in claim 18. Therefore, Applicants submit that Kelly does not render obvious claims 18 and 20.

Claims 28, 30, 31, 33-40, 45, and 47 are rejected as being unpatentable over Briggs. According to the Action, "The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at position 5 and the reference teaches attachment at position 4. These are *per se* obvious ring position isomers and require no specific teaching" (Action, page 15, part 15). Applicants have cancelled claims 31 and 45, thus rendering the rejection of the two claims moot. Applicants point out that all of the compounds disclosed in Briggs are C-4 substituted. There is no teaching or suggestion in Briggs that would motivate one of skill in the art to synthesize and investigate compounds in which the the piperazinyl or any heterocyclyl radical has been moved from the C-4 position to the C-5 position of the indole ring. Briggs discloses exclusively unsubstituted piperazinyl at the C-4 position. Applicants have amended independent claim 28 so as to remove unsubstituted piperazinyl as a possible selection for R^4 or R^5. Briggs does not teach or suggest any of the remaining R^4/R^5 heterocyclic selections in the genus delineated in claim 28, as amended. Therefore, Applicants submit that Briggs does not render obvious claims 5, 14, and 18.

Enclosed is $950 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13425-052001.

Respectfully submitted,

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EXHIBIT A

Solubility experiments

1-phenylsulfonyl-4-piperazinylindole dihydrochloride (Example 7) underwent a low throughput screening solubility (LTS) solubility determination using LC-UV and a gradient at room temperature as follows:

HPLC mobile phase

Mobile phase A: Acetonitrile / Water / Trifluoroacetic acid 50/950/1 (v/v/v)

Mobile phase B: Acetonitrile / Water / Trifluoroacetic acid 990/10/1 (v/v/v)

Gradient profile

Time (min)	%A	%B
0	80	20
3	0	100
5	0	100
5.01	80	20

The solubility was estimated in different media after rotation of a sample consisting of the compound in these media, see Table 2 below. SGF means simulated gastric fluid without enzymes. Table 3 below shows solubility results for 1-[(2,5-dimethoxyphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride (Example 8). Table 4 shows solubility results for compound 4a according to Isaac, i e 2-[1-(naphthalene-1-sulfonyl)-1H-indol-6-yl]-octahydro-pyrrolo[1,2-a]pyrazine. From these Tables below, it could be seen that the solubility of 2-[1-(naphthalene-1-sulfonyl)-1H-indol-6-yl]-octahydro-pyrrolo[1,2-a]pyrazine in SGF, pH 1.2 has a significantly lower solubility (30.5 μg/ml) than both 4-substituted indoles (722 and 217 μg/ml, respectively), implying that the solubility is dependent on the substitution pattern. Hence, one could await different properties of 4-substituted indoles compared to 6-substituted indoles.

Table 2 – Solubility results for Example 7

Medium	Rotation time (h)	Added (mg/ml)	Found µg/ml	Found mg/ml	Found µM	pH of the filtrate
MilliQ (water)	24	20.3	5468	5.47	16030	3.2
SGF, pH 1.3	24	19.8	722	0.72	2116	1.2
0.15 M phosphate buffer, pH 5	24	18.8	215	0.22	630	4.6

Table 3 – Solubility results for Example 8

Medium	Rotation time (h)	Added (mg/ml)	Found µg/ml	Found mg/ml	Found µM	pH of the filtrate
MilliQ (water)	24	3.53	2139	2.14	4884	2.3
SGF, pH 1.2	24	0.45	217	0.22	495	1.3
SGF, pH 6.8	24	0.57	54.7	0.05	125	6.8

Table 4 – Solubility results for 2-[1-(naphthalene-1-sulfonyl)-1H-indol-6-yl]-octahydro-pyrrolo[1,2-a]pyrazine

Medium	Rotation time (h)	Added (mg/ml)	Found µg/ml	Found mg/ml	Found µM	pH of the filtrate
MilliQ (water)	24	0.70	not stable	not stable	not stable	7.0
SGF, pH 1.2	24	0.64	30.5	0.03	70.6	1.4
SGF, pH 6.8	24	0.45	not stable	not stable	not stable	6.8